REMARKS

Pursuant to the Final Office Action dated March 30, 2006, all pending claims, namely claims 1-7, 10-22, 33, 34, 45 and 47-62, stood rejected as being unpatentable over Trogolo et. al. in view of Michael et. al. and Schink et. al. On April 21, 2006, Applicants submitted an extensive, detailed and thoughtful response addressing each of the arguments raised by the Examiner in the Final Office Action. Despite the many remarks and issues set forth in their response, the Examiner seemingly summarily dismissed the same stating that the response did "not place the application in condition for allowance because: as argued by the Applicant the claims recite a microcapsule, and a particle would not render the claim obvious. However, it is the Examiner's position that the particles in the prior art render the claims obvious since the instant claims recite that the microcapsule comprises multiple particles, see claim 22, and uses the two terms 'microcapsules or particle' as equivalents see the specification paragraph [0040]."

Applicants respectfully traverse the Examiner's maintenance of the rejection and request further consideration in light of the foregoing amendments and the following arguments, as well as those arguments set forth in the response of April 21, 2006, which is hereby reiterated and incorporated by reference. To begin with, Applicants wish to express their disappointment in the complete lack of guidance, argument or acknowledgement of Applicants prior arguments in the Advisory Action. Such would be extremely helpful in preparing an appeal, especially if certain of the points raised have successfully rebutted some, but not all, of the grounds of rejection. Knowing which grounds of rejection remain and/or the Examiner's reasoning as to why the arguments were not persuasive would certainly help in focusing the appeal to the remaining issues without reiterating arguments/issues that are no longer of substance.

Furthermore, Applicants are somewhat confused by the Examiner's Advisory Action communication. If Applicants' reading is correct, the Examiner is stating that Applicants' argument for patentability lies in their perceived distinction between the microcapsules and particles whereas the Examiner contends that the two are one and the same, merely terms used interchangeably. Having reviewed the prior Office Actions in this light, it would seem that this paraphrase of the grounds of rejection is correct. If so, then this evidences a lack of understanding and appreciation on the part of the Examiner as to what is claimed and its scope.

As such, and while Applicants believe the claims as presented were abundantly clear, Applicants have now amended the claims in an effort to clarify any confusion and to more succinctly define the invention for purposes on focusing the claim scope for appeal, if necessary.

Specifically, Applicants have amended independent claims 1, 45 and 55 to clearly recite that the critical and inventive aspect is an article of manufacture of a defined composition wherein the article is an antimicrobial additive in the form of a microparticle whose largest dimension is no more than about 500 microns and whose aspect ratio is at least 2 and wherein the composition of matter from which the article is made comprises a hydrophilic polymer having dispersed therein even smaller particles of an inorganic antimicrobial agent comprising antimicrobial metal or metal ions. In essence, Applicants claim particles within a particle, wherein the inner particles are the inorganic antimicrobial agent and the outer particle or encasing particle is the hydrophilic polymer. These "particles in a particle" are then to be used as additives for imparting improved antimicrobial efficacy to a matrix polymer or polymer composition into which they are to be incorporated as compared to the use of the corresponding neat antimicrobial agents (i.e., without the encapsulating or encasing hydrophilic polymer), even at the same loading of antimicrobial agent. While Applicants believe this construction was clear from the claims as originally presented, particularly in light of the specification, they have nonetheless revised the claims for added clarity.

In addition to the foregoing amendments, Applicants have amended each of the dependent claims consistent with the revision to the independent claims and deleted claim 47. No new matter has been entered as the amendments are fully supported by the specification as filed, including, specifically, the Abstract, Paragraphs [0035-0048] and [0056], or are obvious editorial modifications. Applicants believe that the claims, as amended, are clearly distinct from and patentable over the art cited by the Examiner for the reasons previously argued and as follows.

First, Applicants freely acknowledge the prior art teaching of antimicrobial hydrophilic polymer compositions, especially coatings and paste-like compositions, comprising a hydrophilic polymer having dispersed therein antimicrobial agents, including silver zeolites. However, none of the cited art suggest high aspect ratio microparticles of such compositions or the utility of

such microparticles as an alternative to neat antimicrobial agents with the added benefits of enhanced and/or controlled antimicrobial efficacy. Contrary to the Examiner's prior assertion, Applicants are not claiming merely a new use, new function or an unknown, yet inherent, property of a known composition. Rather, Applicants claim a new form of a composition which form provides certain utilities and benefits not evident or obvious from the teachings of the cited references. It is well established that a new form of an old composition, especially where the new form is novel and unobvious, is patentable (See e.g., In re Berry 315 F2d 916, 137 USPQ 353 (CCPA 1963)). Further, new forms of old compositions are likewise patentable if the differences in the utilities of the new forms are substantial and unobvious (See e.g., Chas. Pfizer & Co., Inc. v. Barry-Martin Pharmaceuticals (DCSD Fla. 1965)). Especially pertinent to this discussion is In re Cofer (354 F2d 664, 148 USPQ 268 (CCPA 1966)) wherein claims to a free flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals (See MPEP 2144.04(VII)).

Despite the Examiner's assertion in the Final Rejection that the improved properties are not within the scope of the claims and, therefore, not an issue of examination, the utility and properties are indeed very relevant to the examination of the pending claims. As noted in the above-referenced case law, new and/or different utilities of a new form of an old composition of matter are critical factors to be considered in assessing the patentability of these new forms of an old composition. In any event, the improved properties have been or should have been considered with respect to the patentability of the method claim, claim 45.

To simplify the Examiner's review of the properties and benefits of the claimed antimicrobial additives, Applicants present the following brief description of some of the more significant properties and benefits thereof:

In hydrophobic compositions:

Hydrophobic resins or matrices present a particular problem to inorganic antimicrobial additives that rely upon ion-exchange or dissolution to release or allow for antimicrobial efficacy. Since water is unable to penetrate into the hydrophobic material, only that antimicrobial active at the surface thereof is available to provide antimicrobial activity. Thus,

any antimicrobial agent that is encased or entombed in the hydrophobic matrix is essentially lost unless the surface is worn away to thereby expose the previously encased or entombed antimicrobial particle. Increasing the amount of antimicrobial agent added to the hydrophobic resin will increase the amount of available antimicrobial active; however, it also correspondingly increases the amount of lost antimicrobial agent: if there is more at the surface there is more in the bulk of the polymer as well. Given the high cost of these materials and their tendency to cause discoloration, increasing their level of incorporation is not a commercial option. Using a similar loading of a larger particle size antimicrobial agent presents a larger reservoir of antimicrobial active and better longevity; however, antimicrobial efficacy is lessened due to the lower density across the surface of the substrate and, consequently, fewer release points. Thus, one either trades off performance for life or life for performance as one adjusts the particle size for a given loading of a neat antimicrobial agent.

Applicants overcome this 'either/or' circumstance by effectively increasing the size of the antimicrobial agent through encapsulation or encasement of the antimicrobial agent particle in a suitably hydrophilic polymer microparticle. Specifically, the water absorption and swelling characteristics of the hydrophilic polymer enable the antimicrobial active within the hydrophilic polymer matrix to dissolve and/or be transported within and through the hydrophilic polymer. Thus, as long as a portion of an antimicrobial hydrophilic polymer microparticle touches or is present at the surface of the hydrophobic polymer substrate, all of the antimicrobial active contained therein is available to provide antimicrobial activity. Employing a high aspect ratio microparticle increases the likelihood that a given hydrophilic microparticle will touch the surface and helps minimize any impact the hydrophilic polymer may have on the properties/-performance of the hydrophobic polymer resin into which the microparticles are incorporated. Generally speaking, Applicants can employ less antimicrobial active and provide a higher degree of antimicrobial performance than is achievable with an equivalent loading of the neat antimicrobial agent, i.e., that which is not encased or encapsulated in a hydrophilic polymer microparticle.

To assist the Examiner's understanding in this respect, Applicants submit herewith AgION Technical Memo TM-9 entitled, "Technical Comparison of AgION Antimicrobial to Nanoparticulate Silver" by Doctor Jeffrey A. Trogolo, a co-inventor of the present invention.

Though directed to neat antimicrobial agents, this article clearly teaches and demonstrates the correlation of density and particle size relative to antimicrobial performance and longevity and is directly analogous to the claimed invention.

In addition to the foregoing, the claimed antimicrobial additives also manifest less discoloration as compared to neat antimicrobial agents. As known to those skilled in the art, discoloration is most often associated with chemical interactions between the antimicrobial agent or active and other chemicals in the matrix polymer occurring during the process of incorporating the antimicrobial agent into the polymer matrix, especially in extrusion or melt blending. Though the actual discoloration may not manifest itself immediately, it will become more pronounced over time as the reaction products are exposed to certain environmental conditions, especially UV light. With Applicants' invention, discoloration is essentially limited to the microparticle since, in processing, the antimicrobial agent has little, if any, contact with the matrix polymer as the antimicrobial hydrophilic microparticle is being incorporated therein. In essence, the encapsulating hydrophilic polymer serves as a protective barrier. Also, since less antimicrobial active is needed in order to manifest an equivalent level of bioefficacy and longevity as compared to the neat antimicrobial agent, there is less opportunity for discoloration.

In hydrophilic resins:

While the vast majority of applications for antimicrobial polymers involve hydrophobic polymers, a number of applications allow for or require hydrophilic polymers or coatings. Here one is not concerned with availability of the antimicrobial active, rather one is concerned with release rate and longevity: both of which are directly related to the hydrophilicity or water absorption characteristics of the hydrophilic polymer. Too little water absorption and the rate of release may be too slow to provide good antimicrobial efficacy. Thus one may have extended, long term release, but if too little is releasing, it may be insufficient to protect the substrate against bacterial intrusion. On the other hand, if the degree of hydrophilicity is too high, water absorption will be great and release and transport of the antimicrobial active will readily occur and be uncontrolled. Such high levels of release may result in certain environmental, health and safety issues and/or deplete the reservoir of its antimicrobial actives too quickly so as to render the treated substrate antimicrobially ineffective after a short period of time.

In the former circumstance, Applicants are able to employ a hydrophilic polymer for making the antimicrobial microparticles which has a higher degree of hydrophilicity than the hydrophilic matrix polymer into which the antimicrobial additive is to be incorporated. This has the effect of increasing the rate of release, similar to that effect seen with the use of the claimed antimicrobial microparticles in a hydrophobic resin. Specifically, the rate of release for those microparticles at the surface will be determined by the hydrophilic polymer of the microparticle whereas the rate of release of the microparticles within the bulk of the hydrophilic matrix resin will be determined by the hydrophilic resin. Thus, one is able to ensure good initial release while also ensuring good long term release.

In those applications where the degree of hydrophilicity of the matrix resin is too high, Applicants are able to employ antimicrobial hydrophilic microparticles whose degree of hydrophilicity is less than that of the hydrophilic polymer into which they are to be incorporated. Thus, one is able to slow the rate of release of the antimicrobial agent since it is now a function of the hydrophilic polymer of the microparticle, not the hydrophilic matrix material: thereby increasing the longevity of the antimicrobial polymer.

In following with the foregoing, Applicants' invention allows one to design antimicrobial microparticles for particular applications. Specifically, by simple testing, one is able to assess and determine the release rates for different hydrophilic polymers. Employing this information, one can then design or select a given hydrophilic microparticle for a given application so that its release rate and longevity are consistent with the application and life of the article into which they are incorporated. This is of particular advantage for medical devices, especially short term and long term implanted devices such as catheters.

Certainly, none of the aforementioned advantages, benefits or applications are possible with the compositions of the prior art nor are any of them obvious from or suggested or inferred by the teachings of the cited art. Thus, Applicants claimed antimicrobial additives and method of using the same are clearly patentable.

Finally, as discussed in Applicants' prior responses, Michal et. al. in no way make obvious the claimed antimicrobial hydrophilic microparticles having a dopant incorporated therein. Applicants fail to see where Michal et. al. even suggest, motivate or infer the

combination of a nitric oxide donor, let alone sodium nitrate, and a hydrophilic coating. Certainly, Michal et. al. make no suggestion or inference to render any of its coatings antimicrobial. Even if, somehow, there was a motivation to combine Michal et. al. with Trogolo, it is still not apparent how or where Michal et. al. lead one to combine a hydrophilic polymer with sodium nitrate. Instead, Michal et. al. seem to suggest that the therapeutic agents (of which sodium nitrate is one) and the hydrophilic agents are mutually exclusive additives. Regardless, even if one somehow arrived at the combination of all three required constituents, nothing motivates one to make a microparticle thereof and use the same as an antimicrobial additive for polymer compositions and coatings. Furthermore, nothing would have suggested that the inclusion of the sodium nitrate would have enhanced the initial release of the antimicrobial active agent from the microparticles. In light of the foregoing, nothing has been presented that would even remotely bring into question the patentability of the claims over Michal et. al. and Trogolo et. al.

Conclusion

Applicants believe that the claims as now presented are clearly patentable over the art for the reasons set forth above. Applicants respectfully request that the rejections be withdrawn and the application be passed on to allowance. Should the Examiner persist with the rejections, Applicants request that this amendment be entered for purposes of appeal. Entry is appropriate since the claim amendments certainly narrow and more clearly focus the issues for appeal and are fully consistent with the scope of examination to date.

Respectfully submitted,

Edward K. Welch II
Attorney for Applicant
Registration No. 30,899
IP&L Solutions
4558 Ashton Court
Naples, FL 34112
Tel.: 781-718-9512
e-mail: welched@comcast.net

AgION ANTIMICROBIAL
Excellence in Antimicrobial Solutions

Technical Memo TM-9
May 3, 2005

Technical Comparison of AgION Antimicrobial to Nanoparticulate Silver

Jeffrey A. Trogolo, Ph.D.

Nanoparticulate silver is a recent addition to the group of technologies designed to use silver as an antimicrobial. The strategy uses very fine particles of silver blended into plastics to impart antimicrobial activity. However, the fine particle size limits the available silver reservoir and the particles that are exposed must provide silver by oxidizing and dissolving, a process that is highly variable and very dependent on the environment in which the part is used.

The Reservoir Model

The primary indirect indicator of performance in antimicrobial surface engineering is the quantity of active ingredient available at the surface. This quantity, the silver reservoir in the case of silver based inorganic antimicrobials, can be both calculated and measured. The calculation involves the obvious variables of Ag loading in the antimicrobial additive and the additive loading in the plastic or coating. However, following is an illustration of how the particle size is also a significant variable.

On first thought, the total silver content of the plastic is a logical metric to use to compare particulate antimicrobials. It can easily be calculated by multiplying the Ag content of the particles by the particle loading in the material. However, when that is plotted against the measured silver reservoir available from the surface, determined by performing a serial extraction, the plot in Figure 1 is obtained.

Four different types of antimicrobial additives were used for this experiment ranging in particle size, silver content and loading in the plastic. Based on silver content in the plastic, a logical metric of expected performance, at first glance, there is no correlation to the Ag reservoir, the indicator of performance.

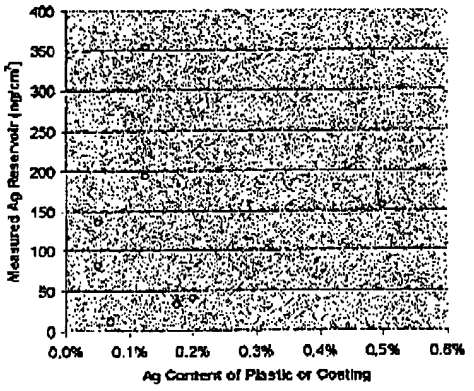

Figure 1: Comparison of the Ag content of the plastic to the available silver measured

through serial extraction. Note the lack of correlation.

Now consider the schematic diagram in Figure 2, in which particles are embedded in a material near the surface. Only the top layer of material, to the depth of one particle diameter, contains available silver. Particles deeper into the polymer are not in contact with the surface and therefore cannot deliver silver and provide efficacy.

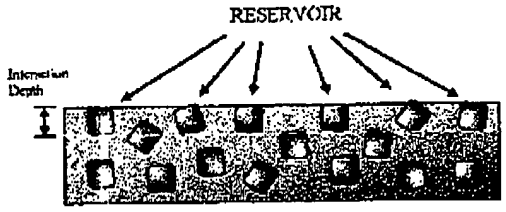

Figure 2: The available silver reservoir in a material containing a particulate additive

Therefore, we can calculate the reservoir in a one square centimeter area with the formula,

$$R\left(\frac{ng}{cm^2}\right) = D(\mu m)\cdot C(\%)\cdot L(\%)\cdot 10^5$$

If the same data from Figure 1 is recalculated to account for particle size as in the equation, the plot in Figure 3 is obtained.

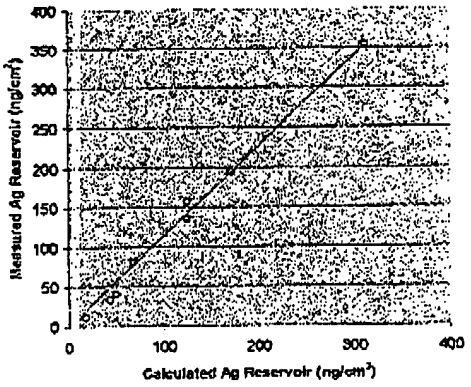

Figure 3: Measured Ag reservoir showing correlation with the reservoir model accounting for additive Ag content, additive loading in the plastic, and particle size.

The calculated reservoir data matched the measured data with a correlation coefficient of 99.6%, indicating a highly predictive model.

Explaining the particle size effect

The reason that particle size has such a strong effect on the accuracy of the model can be illustrated in the diagram in Figure 4. The diagram represents two plastic parts that contain the same loading of additive, one large particle size material, one smaller particle size material. In the diagram, the combined area of the two dimensional particles (circles) in the top material is equal to that in the bottom material, which serves as an analogy to the three dimensional case of equal loading, but different particle size.

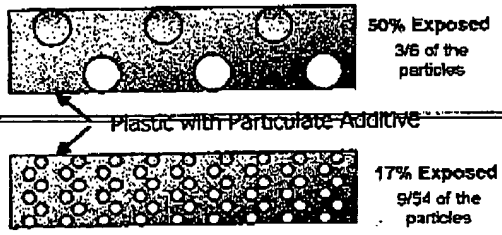

Figure 4: Schematic diagram illustrating the influence of particle size on surface access relative to loading. These diagrams represent identical "loadings". In the top figure 50% of the powder added is exposed, in the bottom figure, only 17% is exposed.

From the diagram it is apparent that, for the larger particles, a greater percentage of the material added to the plastic is in contact with the surface (shaded), than for the smaller particles.

We can see the effect of this difference by measuring the silver reservoir in a variety of samples with different particle sizes and loadings of different additive

grades. The chart in Figure 5 presents the calculated and measured silver reservoir in samples loaded to 2% with an antimicrobial having a submicron particle size and two different silver contents, and AgION grades with larger particle size and lower silver content.

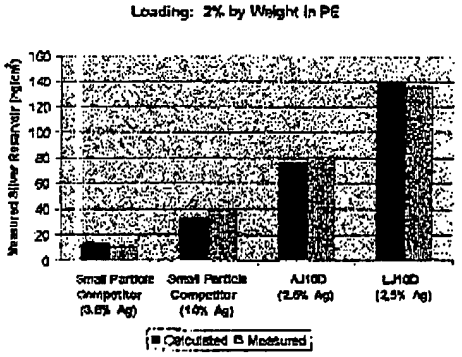

Figure 5: Test results showing how smaller particles provide less available silver even though the particles have higher Ag content

The small particle grades have significantly higher silver loading, yet fail to release nearly as much silver as the lower Ag content AgION grades. The clearest example of the particle size effect in this diagram is the comparison of AgION grades AJ10D and LJ10D. The two grades differ only in particle size and the larger LJ10D grade provides nearly twice the silver reservoir.

Nanoparticulate silver materials range in particle size, but are generally smaller than 100 nm in diameter. Typical grades are 25-70 nm in diameter, which as demonstrated above, results in only a small portion of the additive being exposed at the surface. Using the same model as described above and comparing nanoparticulate silver to AgION products, the value of an optimized particle size becomes apparent (see Figure 7).

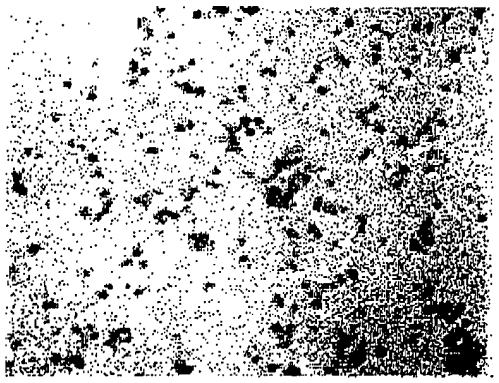

Figure 6: Transmission Electron Microscope image of nanoparticulate silver showing the very small particle size.

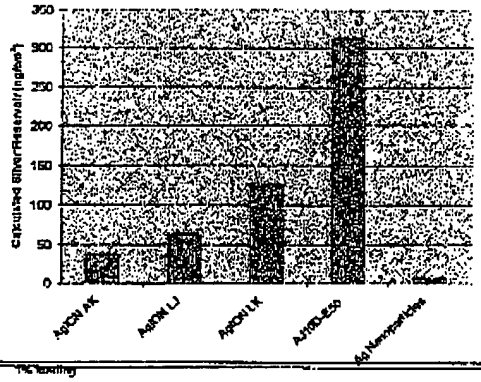

Figure 7: The available silver reservoir for AgION and nanoparticulate silver (at 1% loading in a plastic) demonstrating that the AgION particles shave much more available silver.

Furthermore, for the silver to become ionic, which is required to control bacteria, the metal particles must oxidize and then the oxide must dissolve. Metallic silver dissolution by this mechanism doesn't readily occur, obviously, since we know silver jewelry and silverware don't dissolve. In general, dissolution is a poor release mechanism because it if very sensitive to the environment in which the treated part resides. Temperature, flow rate, pH and

other dissolved species have a significant effect on the kinetics of dissolution. In particular, acidic solutions greatly increase the solubility of silver oxide, and therefore, can deplete the surface of silver very quickly.

To test the stability of the silver nanoparticles, samples of ABS plastic containing nanoparticulate silver were soaked in a 0.7% to extract all the exposed silver and determine the available reservoir. One set of as-molded samples were soaked for 20 min and 24 hours in Coca Cola, another set in orange juice for the same times. The results of the experiment are shown in Figure 8, and demonstrate that the silver is rapidly dissolved from the surface in a very short time under conditions that are not unusual in normal applications.

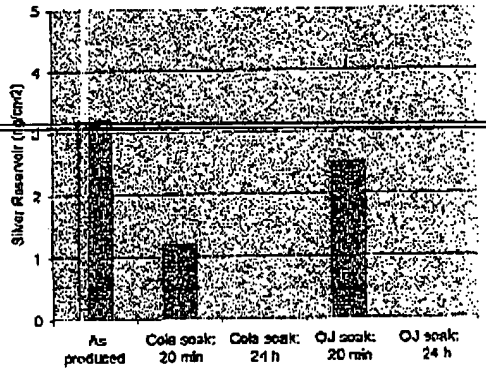

Figure 8: Depletion of the nanoparticulate silver reservoir in ABS plastic by common acidic beverages.

The vulnerability of nanoparticulate silver to environmental conditions greatly limits its use in "real-world" applications. Few products can be guaranteed to experience only a narrow range of environmental conditions.

In conclusion, the particle size and metallic form of nanoparticulate silver makes it unsuitable for use in applications where varying chemistry, challenging microorganisms, wet environments or long term applications – all environments in which AgION Antimicrobial regularly demonstrates high levels of efficacy.